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PATENT

ATTORNEY DOCKET NO.: 50657-05302USP1

183

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Hermann et. al.	§	Art Unit:	1646
Serial No.:	09/175,713	§	Examiner:	Janet L. Andres
Filed:	October 20, 1998	§		
Entitled:	Chemokines with Amino-Terminal Modifications	§		

Assistant Commissioner for Patents
Washington, DC 20231

Dear Sir:

CERTIFICATE OF MAILING 37 C.F.R. 1.8

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APPEAL BRIEF PURSUANT TO 37 C.F.R. §§ 1.191 AND 1.192

This appeal brief is filed pursuant to the Applicant's appeal from the decision of the Patent Office to the Board of Patent Appeals and Interferences filed on October 18, 2001.

1. REAL PARTY IN INTEREST

The real party in interest is Genetics Institute, Inc. having a place of business at 87 Cambridge Park Drive, Cambridge, Massachusetts 02140.

2. RELATED APPEALS AND INTERFERENCES

Appellants knows of no other appeals and interferences which will directly affect or be directly affected by or which have a bearing on the Board's decision in the pending appeal.

3. STATUS OF CLAIMS

At the time of the mailing of the Advisory Action, claims 1-14, 17 and 18 were pending in this application. In the Advisory Action, claims 1-14, 17 and 18 were rejected. An Amendment filed on October 18, 2001 amended claims 6-9 in response to the rejection of these claims as indefinite in the Advisory Action (*see* below). Assuming entry of the amendments below, the status of the claims are as follows: Claims 1-14, 17 and 18 are currently pending. A copy of the pending claims is attached herein as Appendix 1. The pending claims stand rejected under 35 U.S.C. § 112, ¶ 1 as lacking sufficient written description and enablement. Appellant appeals the rejection of claims 1-14, 17 and 18.

4. STATUS OF AMENDMENTS

Appellants submitted amendments to the pending claims under the provisions of 37 C.F.R. § 1.116 on July 2, 2001, subsequent to the Final Rejection mailed May 2, 2001. These amendments canceled pending claims 15, 16, and 19-47. A copy of the July 2, 2001 amendments are attached herein as Appendix 2. In an Advisory Action mailed on July 30, 2001, the Patent Office indicated that the proposed amendments would be entered upon filing of the Notice of Appeal and an Appeal Brief. A copy of the Advisory Action is attached herein as Appendix 3. An Amendment dated October 18, 2001 amending claims 6-9 was filed in response to the Advisory Action. A copy of the October 18, 2001 Amendment is attached herein as Appendix 4. The claims at Appendix 1 of this Appeal Brief reflect the cancellation of claims 15, 16, 19-47 and the amendment of claims 6-9.

5. SUMMARY OF THE INVENTION

The invention is directed generally to amino-terminal-modified (N-terminal-modified) chemokines and the use of such chemokines to inhibit the interaction between chemokine receptors and naturally occurring ligands of those receptors. Application at p.1, lines 11-13. The invention provides recombinant polynucleotide sequences encoding chemokines having additional amino acids or other chemical groups attached to their amino terminii, and the use of such N-terminal-modified chemokines as research tools for identifying chemokine receptors, as vaccine adjuvants, as agents for the chemotactic recruitment of migratory cells, as agents for the stimulation or inhibition of angiogenesis, as agents against autoimmune diseases and inflammation, and as agents to inhibit the binding of HIV to certain receptors and the infection of susceptible cells by HIV. Application at p.1, line 14-21.

The pending claims are drawn to compositions comprising isolated polynucleotides encoding amino-terminal-modified chemokines comprising at least one methionine, at least one aminooxypentane residue, or at least one GroHEK peptide covalently attached to the amino terminus of the chemokine, wherein the chemokine is selected from a group consisting of a finite number of chemokines well-known to one of ordinary skill in the art. The claims also read on the expression of the amino-terminal-modified chemokines in a host cell.

6. **ISSUE**

A. Whether Appellants' invention as claimed lacks sufficient description under 35 U.S.C. § 112, paragraph 1.

B. Whether Appellants' invention as claimed lacks enablement under 35 U.S.C. § 112, paragraph 1.

7. GROUPING OF CLAIMS

Appellants respectfully submit that the rejected claims do not stand or fall together. As shown below, Appellants consider certain groupings of claims to be separately patentable. Appellants have grouped the claims as shown below only for the purposes of isolating and reducing issues for this appeal. The groupings shown below are not to be considered the only group or individual claims that are separately patentable.

The claims can be considered in two groups. Group 1 comprises claims 1-5 and 10-14, 17 and 18 which read on compositions comprising an isolated polynucleotide encoding an amino-terminal-modified chemokine. Group 2 comprises claims 6-9 which read on compositions comprising an isolated polynucleotide encoding an amino-terminal-modified chemokine where the polynucleotide is selected from a group consisting of specifically defined polynucleotides. Claims 6-9 are of a narrower scope than the broad independent claim that they depend from.

8. ARGUMENT

A. Introduction

The Examiner has rejected claims 1-14, 17 and 18 as lacking sufficient written description and lacking enablement under 35 U.S.C. § 112, paragraph 1.

Claims 1-14, 17 and 18 are drawn to a specifically enumerated set of amino-terminal modified chemokines that are sufficiently described in the specification to convey to one of ordinary skill in the art that Appellants were in possession of the claimed invention at the time the application was filed.

Furthermore, Appellants have provided more than enough detail in the specification to enable one of ordinary skill in the art to practice the invention as claimed. Appellants appeal the Examiner's rejection of claims 1-14, 17 and 18 because (i) the subject matter of the claims is supported by the disclosure of the application and (ii) the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one of ordinary skill in the art to make and use the claimed invention.

B. Applicable Law

Written Description:

Courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that [the applicant] invented what is claimed." *In re Gostelli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989). An applicant must convey with **reasonable clarity** to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991) (emphasis added).

There is a **strong presumption** that an adequate written description of the claimed invention is present in the specification as filed. *In re Wertheim*, 541 F.2d 257, 262 (C.C.P.A. 1976). In other words, a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner rebut the presumption. See, e.g., *In re Marzocchi*,

439 F.2d 220, 224 (C.C.P.A. 1971). The examiner therefore has the burden of presenting by a preponderance of the evidence why a person in the art would not recognize in an applicant's disclosure, a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d at 263.

Enablement:

The standard for determining whether the specification meets the enablement requirement was cast in the United States Supreme Court decision of *Mineral Spectrum v. Hyde*, 242 U.S. 261, 270 (1916), which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *Id.*; See also *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988) (The test of enablement is whether one reasonably skilled in the art could make and use the invention from the disclosures in the patent **coupled with information known in the art** without undue experimentation."). Indeed, a patent need not teach and preferably omits what is well known in the art. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991).

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983). There are many factors to be

considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;
(B) The nature of the invention:
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d at 737 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). The Court held that the specification was enabling with respect to the **claims** at issue and found that "there was considerable direction and guidance" in the specification; there was "high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." *Id.* at 740. It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. *Id.* The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all of the above noted factual consideration. *Id.* at 737.

As long as the specification discloses at least one method for making and using the claimed

invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970).

C. Application of the law to the facts

1. <u>The subject matter of claims 1-5, 10-14, 17 and 18 is supported by the disclosure</u>

Claims 1-5, 10-14, 17 and 18 have been rejected as lacking sufficient written description under 35 U.S.C. § 112, paragraph 1. In a previous Office Action Examiner rejected pending claims 1-14, 17 and 18 because "there is insufficient guidance to allow one of skill to identify other species that would have the same functional characteristics as the disclosed species." *See* Final Office Action dated May 2, 2001 at p.3. In the response Appellants argued that "[b]y requiring that the functional characteristics of the claimed compositions be disclosed, Examiner has impermissibly read a (functional) limitation into the claims. The scope of pending claims 1-14, 17 and 18 read on compositions comprising a chemokine (from an enumerated list) that is modified at its amino-terminus. The invention as claimed does not require knowledge of the structural and functional characteristics of the amino-terminal modified chemokines in order to practice the claimed invention." *See* Response to Final Office Action at p.4. In the advisory action dated July 30, 2001, Examiner states that "because Applicant states on page one of the specification that the invention relates to amino-terminal modified chemokines and the use of such chemokines to inhibit the interaction between chemokine receptors and naturally occurring ligands," the claims must therefore be viewed as reading on the functional characteristics of the amino-terminal-modified chemokines. *See* Advisory Action at p.2.

Just because the specification states that "[t]he present invention relates **generally** to amino-terminal-modified chemokines **and** the use of such chemokines to inhibit the interaction between chemokine receptors and naturally occurring ligands of those receptors" does not mean that a functional limitation can be read into the pending claims as they are currently drafted. *See* Specification at p.1, lines 11-13. When the claims specifically read on compositions comprising a chemokine (from an enumerated list) that is modified at its amino-terminus, it is impermissible for the Examiner to read a functional limitation into the claims, just because the specification also supports claims reading on the functional characteristics of modified chemokines.

In order to comply with the written description requirement, an applicant need only convey with **reasonable clarity** to those skilled in the art that, as of the filing date sought, he was in possession of the invention. Appellants have more than met the requirement for "reasonable clarity." Appellants have provided sufficient detail in the specification in Example 1, which would enable one of ordinary skill to recognize that Appellants were in possession of the subject matter of the invention in claims 1-5, 10-14, 17 and 18. Example 1 sets forth specific details of the methods used to construct exemplary amino-terminal-modified chemokines, namely GroHEK/hSDF-1α, GroHEK/hSDF-1β, met-hSDF-1α and met-hSDF-1β. The Example illustrates how to add a specific moiety (methionine or GroHEK) to the amino-terminal end of a chemokine having a known sequence. The chemokines claimed in claims 1-5, 10-14, 17 and 18 belong to the C-C, CXC or CX3C class of chemokines (*See* Specification at p.2) and were well known in the art by their common laboratory names long before the filing date of the

instant application. *See* references cited in Specification at p.17, lines 21-25, and p.18, lines 1-2. Similarly, modification of the N-terminus of an amino acid with an aminooxypentane residue was also well known in the art at the time of the filing of Appellant's application. *See* Specification at p.18, lines 24-25, and p.19, lines 1-4. Therefore, coupled with information known in the art, Appellants have described a procedure of generating chemokine compositions modified at the amino-terminus and those of ordinary skill in the art would readily recognize that Appellants were in possession of the invention **as claimed**, i.e., a specifically enumerated list of chemokines having known sequences that are modified with GroHEK, methionine or aminooxypentane at the amino-terminus. In sum, given the description of the invention in the Examiner has not met her burden of presenting by a preponderance of the evidence why a person in the art would not recognize in Appellant's disclosure, a description of the invention as **defined by the claims**.

2. The subject matter of claims 6-9 is supported by the disclosure

All of the above arguments under section C.1. apply to claims 6-9. In addition however, claims 6-9, as amended, are separately patentable from claims 1-5, 10-14, 17 and 18 because they read on a narrower subset of modified chemokines than claims 1-5, 10-14, 17 and 18. The narrow subset of modified chemokines in claims 6-9 are defined by SEQ ID NOs and ATCC accession numbers, and convey with more than "reasonable clarity" that Appellants were in possession of the invention claimed in claims 6-9 as of the filing date of the instant application.

3. The subject matter of claims 1-5, 10-14, 17 and 18 is enabled by the disclosure

Claims 1-5, 10-14, 17 and 18 have been rejected under 35 U.S.C. § 112, paragraph 1 as not being enabled by the disclosure. In the Advisory Action, Examiner states that "[w]hat is set forth in the specification as Applicant's invention are amino-terminally modified molecules that are inhibitors of receptor/ligand binding....[O]ne of skill in the art **would be able to make** the modified proteins, but would not be able to predict which could actually be used. It is this lack of predictability ... that renders the required experimentation undue." Advisory Action at p.2 (emphasis added). In sum, Examiner concedes that the claimed invention can be made, but expresses reservations as to whether the disclosure enables the use of the invention.

The Examiner's characterization of Appellants's invention as "amino-terminally modified molecules that are inhibitors of receptor/ligand binding" is incomplete. As set forth in the Specification at pages 25-32, the amino-terminal-modified chemokines of the instant invention have several uses including, as a tool for identifying cells expressing receptors for the chemokine, as vaccine adjuvants, to enhance the activity of antigen-presenting cells, to affect the chemotactic recruitment of migratory cells and to affect the nature of chemokine-receptor interactions. In addition, Examples 2-6 provide protocols for the various uses of the amino-terminal-modified chemokines of the instant invention. Under *In re Wands*, if there is considerable direction and guidance in the specification, if there is a high level of skill in the art at the time the application was filed, and if all of the methods needed to practice the invention are either disclosed in the specification or are well known, then the specification is enabling with respect to the claims at issue. All of the *In re Wands* considerations are applicable in the instant

case, i.e., there is considerable guidance in the specification, there was high level of skill in the art at the time the application was filed and all of the methods needed to practice the claimed invention are either disclosed or well known in the art. Appellants have provided details in the specification and in the form of working examples to enable one of ordinary skill in the art to practice the claimed invention. In addition, as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. In the instant case, Appellants have disclosed several working examples to illustrate the various uses of the invention.

Examiner has already conceded that the claims which read on the "making" of the amino-terminal modified chemokines are enabled by the specification of the application. However Examiner states that one of ordinary skill in the art would not be able to predict which of the possible modified chemokines would function in accordance with the invention. This statement by Examiner incorrectly states the enablement requirement under 35 U.S.C. § 112. The test of enablement is whether one reasonably skilled in the art could make and use the invention from the disclosures in the application coupled with information known in the art without undue experimentation. The enablement requirement does not require that the disclosure provide any type of prediction with respect to the end results obtained from practicing the invention, which is what Examiner indicates is missing from the disclosure. In the instant case, Appellants have provided a detailed road map to enable one of ordinary skill in the art to practice the invention without undue experimentation. Appellants therefore submit that the "use"

aspect of the claimed invention has also been met.

4. The subject matter of claims 6-9 is enabled by the disclosure

All of the above arguments under section C.3 apply to claims 6-9. In addition however, claims 6-9, as amended, are separately patentable from claims 1-5, 10-14, 17 and 18 because they read on a narrower subset of modified chemokines than claims 1-5, 10-14, 17 and 18. The narrow subset of modified chemokines in claims 6-9 are defined by SEQ ID NOs and ATCC accession numbers that are disclosed in the specification and therefore enable one of ordinary skill in the art to practice the invention claimed in claims 6-9.

9. CONCLUSION

For the reasons set forth above, appealed claims 1-14, 17 and 18 satisfy the written description and enablement requirements set forth under 35 U.S.C. § 112, paragraph 1. Accordingly the final rejection of pending claims 1-14, 17 and 18 should be reversed.

Appellant is submitting a check in the amount of $320 as payment of the Appeal Brief fee as required by 37 C.F.R. § 1.17(c). The Commissioner is hereby authorized to charge Deposit Account No. 10-0447, reference 50657-05302USP1 for any additional fees inadvertently omitted, which may be necessary now or during the pendency of this application, except for the issue fee.

In accordance with 37 C.F.R. § 1.192(a), this brief is submitted in triplicate.

PATENT
ATTORNEY DOCKET NO.: 50657-05302USP1

Respectfully submitted,

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Date: December 18, 2001

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Appendix 1

Claims Pending on Appeal

1. (Amended) A composition comprising an isolated polynucleotide encoding an amino-terminal-modified chemokine, wherein the amino-terminal-modified chemokine comprises at least one methionine, at least one aminooxypentane residue, or at least one GroHEK peptide covalently attached to the amino terminus of the chemokine, and wherein the chemokine is selected from the group consisting of SDF-1α, SDF-1β, IP-10, Mig, GROα, GROβ, GROγ, interleukin-8, PF4, ENA-78, GCP-2, PBP, CTAP-III, β-thromboglobulin, NAP-2, C10, DC-CK1, CKα1, CKα2, MCP-1, MCP-2, MCP-3, MCP-4, MIP-1α, MIP-1β, lymphotactin, ATAC, eotaxin, eotaxin-2, I-309, HCC-1, HCC-2, HCC-3, LARC/MIP-3α, MIP-3β, PARC, TARC, 6Ckine, ELC, SLC, CKβ4, CKβ6, CKβ7, CKβ8, CKβ9, CKβ11, CKβ12, CKβ13, and CX3C.

2. The composition of claim 1 wherein the amino-terminal-modified chemokine comprises at least one methionine covalently attached to the amino terminus of the chemokine.

3. The composition of claim 1 wherein the amino-terminal-modified chemokine comprises at least one aminooxypentane residue covalently attached to the amino terminus of the chemokine.

4. The composition of claim 1 wherein the amino-terminal-modified chemokine comprises at least one GroHEK peptide covalently attached to the amino terminus of the chemokine.

5. (Amended) A composition comprising an isolated polynucleotide encoding an amino-terminal-modified chemokine, wherein the amino-terminal-modified chemokine comprises at least one methionine, at least one aminooxypentane residue, or at least one GroHEK peptide covalently attached to the amino terminus of the chemokine, and wherein the amino-terminal-modified chemokine is derived from a chemokine selected from the group consisting of SDF-1α, SDF-1β, IP-10, Mig, GROα, GROβ, GROγ, interleukin-8, PF4, ENA-78, GCP-2, PBP, CTAP-III, β-thromboglobulin, NAP-2, C10, DC-CK1, CKα1, CKα2, MCP-1, MCP-2, MCP-3, MCP-4, MIP-1α, MIP-1β, lymphotactin, ATAC, eotaxin, eotaxin-2, I-309, HCC-1, HCC-2, HCC-3, LARC/MIP-3α, MIP-3β, PARC, TARC, 6Ckine, ELC, SLC, CKβ4, CKβ6, CKβ7, CKβ8, CKβ9, CKβ11, CKβ12, CKβ13, and CX3C.

6. (Amended) The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:6;

(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the polynucleotide encoding met-hDSF-1α deposited under accession number ATCC 98506;

(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:10;

(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 10;

(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and

(f) a polynucleotide capable of hybridizing at either (i) 4xSSC at 65°C or (ii) 50% formamide and 4XSSC at 42°C, to any one of the polynucleotides specified in (a)-(e) above.

7. (Amended) The composition of claim 1 wherein the polynucleotide is selected from the group

consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the polynucleotide encoding met-hDSF-1β deposited under accession number ATCC 98506;

(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:11;

(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 11;

(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and

(f) a polynucleotide capable of hybridizing at either (i) 4xSSC at 65°C or (ii) 50% formamide and 4XSSC at 42°C, to any one of the polynucleotides specified in (a)-(e) above.

8. (Amended) The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8;

(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the polynucleotide encoding GroHEK/hSDF-1α deposited under accession number ATCC 98508;

(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:12;

(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 12;

(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and

(f) a polynucleotide capable of hybridizing at either (i) 4xSSC at 65°C or (ii) 50% formamide and 4XSSC at 42°C, to any one of the polynucleotides specified in (a)-(e) above.

9. (Amended) The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the polynucleotide encoding GroHEK/hSDF-1β deposited under accession number ATCC 98509;

(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:13;

(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 13;

(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and

(f) a polynucleotide capable of hybridizing at either (i) 4xSSC at 65°C or (ii) 50% formamide and 4XSSC at 42°C, to any one of the polynucleotides specified in (a)-(e) above.

10. A composition of claim 1 wherein the polynucleotide is operably linked to an expression control sequence.

11. The composition of claim 10 wherein the polynucleotide is further operably to a sequence directing secretion if the expressed amino-terminal-modified chemokine.

12. A host cell transformed with a composition of claim 10.

13. The host cell of claim 12, wherein the cell is a mammalian cell.

14. A process for producing an amino-terminal-modified chemokine, which comprises:

(a) growing a culture of the host cell of claim 12 in a suitable culture medium; and
(b) purifying the amino-terminal-modified chemokine from the culture.

17. A composition comprising an isolated polynucleotide encoding an amino-terminal-modified chemokine, wherein the chemokine binds the fusin/CXCR4 chemokine receptor.

18. A composition comprising an isolated polynucleotide encoding an amino-terminal-modified chemokine, wherein the amino-terminal-modified chemokine is a more effective inhibitor of HIV infection than the corresponding unmodified chemokine.

PATENT APPLICATION
ATTORNEY DOCKET NO.: 50657-05301USP1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Herrmann et. al.	§	Art Unit:	1646
Serial No.:	09/175,713	§	Examiner:	Janet L. Andres
Filed:	October 20, 1998	§		
Entitled:	Chemokines with Amino-Terminal Modifications	§		

Assistant Commissioner for Patents
Washington, DC 20231

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Signature

RESPONSE TO OFFICE ACTION MAILED MAY 2, 2001

In response to the Office Action mailed May 2, 2001, Applicants respond as follows:

AMENDMENTS

In the claims:

Please cancel claims 15, 16, and 19-47.

REMARKS

Claims 1-14, 17 and 18 are pending in the application. Claims 1-14, 17 and 18 are rejected. Claims 15, 16, and 19-47 drawn to a non-elected invention have been canceled pursuant to Examiner's request. Applicants reserve the right to file a divisional application or take such other

appropriate action as deemed necessary to protect the invention of Groups II-VIII. By canceling the claims in Groups II-VIII, Applicants do not hereby waive any rights in the inventions of Groups II-VIII.

Appendix A at page 9 of this Response lists all pending claims for Examiner's convenience.

RESPONSE TO REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-14, 17, and 18 are rejected under 35 U.S.C. § 112, first paragraph, as lacking sufficient written description. In making the rejection, the Examiner states the following:

> Applicant's arguments have been fully considered but have not been found to be persuasive. The Examiner agrees that Applicant has described a method for producing four amino-terminally-modified proteins. Such methods are standard in the art. As stated in the previous office action, however, Applicant has disclosed the functional characteristics of one species, while the claims are drawn to a genus of modified chemokines.
>
> In determining that two species of chemical compound were insufficient to describe a genus, *In re Gostelli* does not set forth requirements for written description. *Vas-Cath, Inc. v. Mahurkar* uses the phrase "reasonable clarity" and explains that the purpose of written description is to convey to those of skill that he or she was in possession of the claimed invention at the time of filing. The disclosure of how to make four examples and of the functional characteristics of one does not serve to convey with "reasonable clarity" that Applicant was in possession of the invention as broadly claimed. Applicant has disclosed the functional characteristics of one species. As stated in the previous Office Action, there is insufficient guidance to allow one of skill to identify other species that would have the same functional characteristics as the disclosed species. Thus Applicant has not described the essential characteristics of the claimed genus.
>
> ....
>
> Here, the chemokines are not structurally related, the claimed modifications are not structurally related, and the claims, since they are drawn to compositions comprising the modified chemokines, are not limited to particular modified chemokines, and as discussed in the previous office action, the art is unpredictable.

Applicants respond as follows:

Applicants respectfully disagree with Examiner's conclusion that the subject matter of claims 1-14, 17, and 18 is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention, at the time the application

was filed.

Whenever the issue of written description arises during the prosecution of a patent application, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed. The subject matter of the claim *need not be described literally*. M.P.E.P. § 2163.02 (emphasis added). In examining the sufficiency of a patent application disclosure to support a generic or subgeneric claim, "it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language.'" *In re Grimme*, 124 U.S.P.Q. 499, 501 (C.C.P.A. 1960).

Examiner states that although the claims are drawn to a genus of modified chemokines, "there is insufficient guidance in the disclosure to allow one of skill to identify other species that would have the same functional characteristics as the disclosed species." *Office Action* at p.3. However, rejected claims 1-14, 17 and 18 are drawn to a specifically enumerated set of amino-terminal modified chemokines. In other words, the chemokines used as the starting material for the amino-terminal modified compositions of the present invention are well known to one of ordinary skill in the art, i.e, their nucleotide and amino acid sequences are well known to those of ordinary skill. Upon reading the method set out in Example 1 at page 42 of the Specification, one of ordinary skill in the art would readily recognize that Applicants were in possession of the invention claimed in Claims 1-14, 17 and 18. Example 1 describes the process of attaching an N-terminal moiety to the amino-terminal end of a chemokine. The process is described in great detail and can be easily adapted for use with other

chemokines by one of ordinary skill. Example 1 at page 43 further describes the detailed purification of an exemplary amino-terminal modified chemokine, which can be adapted for use with other amino-terminal modified chemokines. In sum, the disclosure in the patent application provides the level of written description necessary for one of ordinary skill to recognize that the Applicants were in possession of the subject matter of the invention at the time of filing of the application.

Examiner's statement that "there is insufficient guidance in the disclosure to allow one of skill to identify other species that would have the same functional characteristics" is incongruous in light of the fact that claims 1-14, 17 and 18, are drawn to the composition comprising modified chemokines, rather than to their functional characteristics. One of ordinary skill in the art would not be required to "identify other species that would have the same functional characteristics as the disclosed species" because claim 1 reads on a specific set of modified chemokines, the chemokine components of which are well know in the art. By requiring that the functional characteristics of the claimed compositions be disclosed, Examiner has impermissibly read a (functional) limitation into the claims. The scope of pending claims 1-14, 17 and 18 read on compositions comprising a chemokine (from an enumerated list) that is modified at its amino-terminus. The invention as claimed does not require knowledge of the structural and functional characteristics of the amino-terminal modified chemokines in order to practice the claimed invention. Applicants have provided sufficient detail in the specification in Example 1, which would enable one of ordinary skill to recognize that Applicants were in possession of the subject matter of the invention in claims 1-4, 17, and 18.

Claims 1-14, 17, and 18 are also rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement commensurate with the scope of the claims. In making the rejection, the Examiner states the following:

> Applicant has not, ..., provided sufficient guidance for one of skill to use the invention commensurate with the scope of the claims. Applicant has provided working examples for one modified chemokine. Thus the identification of one member of this diverse genus does not provide sufficient guidance by which other species that would function as claimed could be identified; it is clear that the results of the claimed modification are not predictable.
>
> ....
>
> Since there are many possible encompassed species, since Applicant has disclosed the functional characteristics of only one, and since Applicant has not provided any guidance by which other functional species might be identified, and since the art teaches that the outcome of such modifications is not predictable, one of skill would not be able to predict which of the many possible species that meet the limitations of the claims would actually be functional that renders the required experimentation undue.

Applicants respectfully disagree with Examiner's conclusions that the specification does not enable a person skilled in the art to practice the invention commensurate in scope with the claims. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent *coupled with information known in the art*, without undue experimentation. *United States v. Telectronics, Inc.*, 8 U.S.P.Q.2d 1217, 1233 (Fed. Cir. 1988) (emphasis added). A patent need not teach and preferably omits what is well known in the art. *In re Buchner*, 18 U.S.P.Q.2d 1331. 1332 (Fed. Cir. 1991).

All that is required to make and use the invention claimed in claims 1-14, 17 and 18 is knowledge of the nucleotide sequence of the list of chemokines enumerated in claim 1, along with a method of producing the amino-terminal modified form of one of the enumerated chemokines. The

chemokines enumerated in claim 1 were well known in the art at the time of Applicants' invention. *See Specification* at pages 2-3. Therefore, Applicants are not required to provide in their disclosure what is already well known in the art.

As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). Applicants have followed the mandate of *In re Fisher*, and provided a detailed example (Example 1) for making and using the claimed invention. The methods described in Example 1 can be used for all of the enumerated chemokines in claim 1 using the knowledge of the nucleotide sequences of the chemokines described in the prior art, together with the method of modifying the amino-terminal end of the chemokine as discussed in Example 1 of the Specification.

As stated earlier, the invention as claimed *does not require* knowledge of the structural and functional characteristics of the amino-terminal modified chemokines in order to practice the claimed invention. Therefore, Applicants find Examiner's rejection of the claims as lacking enablement because of the absence of functional characteristics of the amino-terminal chemokines in the disclosure, to be without merit. Claim 1 encompasses compositions comprising a specific list of chemokines enumerated in the claim. Knowledge of the nucleotide sequence of the chemokines (known in the prior art) coupled with a method of modifying the amino-terminal (provided in the disclosure) allows one of ordinary skill to make and use the invention in a manner commensurate with the scope of the claims.

RESPONSE TO REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 6-9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In making the rejection, the Examiner states the following:

> The rejection of claims 6-9 as indefinite in the recitation of "amino-terminal fragment" and "stringent conditions" is maintained. Fragments are not defined on p. 20; examples are presented but there are no actual limitations as to what constitutes a fragment. Similarly, what is presented on p. 22 is an example, not a definition, of stringent conditions.

Applicants respond as follows:

Applicants respectfully disagree with Examiner 's statements that the terms "fragments" and "stringent hybridizing conditions" are not defined at pp. 20 and 22 of the Specification respectively. The statement at page 20 which states "such fragments retain the desired activity of the amino-terminal-modified chemokine or modify it to create a desired activity" is in fact, a definition of the term "fragments." Similarly lines 12-19 at page 22 provide a definition for the terms "stringent conditions" and "highly stringent conditions." Specific temperatures and salt concentrations of the hybridization and wash buffers are provided in addition to the statement that the hybridizing polynucleotides are required to be at least 70% homologous by sequence identity with the polynucleotide of the present invention to which they hybridize. Therefore, the meanings of the terms "fragments" and "stringent hybridizing conditions" are apparent from the specification, and the metes and bounds of the invention claimed in claims 6-9 can be readily ascertained by one of ordinary skill in the art.

CONCLUSION

Applicant has addressed all of the Examiner's rejections. Based on the arguments above, Applicant believes that all of the claims are now in condition for allowance and respectfully requests that the Examiner grant such an action. If any questions or issues remain in the resolution of which the Examiner feels will be advanced by a conference with the Applicant's attorney, the Examiner is invited to contact the attorney at the number noted below.

It is believed that no fees are due as a result of this Reply. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 10-0447 (Reference No.: 50657-05302USP1).

Respectfully submitted,
JENKENS & GILCHRIST,
A Professional Corporation

Lekha Gopalakrishnan
Reg. No.: 46,733

Date: July 2, 2001

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Appendix A

List of Pending Claims

1. (Amended) A composition comprising an isolated polynucleotide encoding an amino-terminal-modified chemokine, wherein the amino-terminal-modified chemokine comprises at least one methionine, at least one aminooxypentane residue, or at least one GroHEK peptide covalently attached to the amino terminus of the chemokine, and wherein the chemokine is selected from the group consisting of SDF-1α, SDF-1β, IP-10, Mig, GROα, GROβ, GROγ, interleukin-8, PF4, ENA-78, GCP-2, PBP, CTAP-III, β-thromboglobulin, NAP-2, C10, DC-CK1, CKα1, CKα2, MCP-1, MCP-2, MCP-3, MCP-4, MIP-1α, MIP-1β, lymphotactin, ATAC, eotaxin, eotaxin-2, I-309, HCC-1, HCC-2, HCC-3, LARC/MIP-3α, MIP-3β, PARC, TARC, 6Ckine, ELC, SLC, CKβ4, CKβ6, CKβ7, CKβ8, CKβ9, CKβ11, CKβ12, CKβ13, and CX3C.

2. The composition of claim 1 wherein the amino-terminal-modified chemokine comprises at least one methionine covalently attached to the amino terminus of the chemokine.

3. The composition of claim 1 wherein the amino-terminal-modified chemokine comprises at least one aminooxypentane residue covalently attached to the amino terminus of the chemokine.

4. The composition of claim 1 wherein the amino-terminal-modified chemokine comprises at least one GroHEK peptide covalently attached to the amino terminus of the chemokine.

5. (Amended) A composition comprising an isolated polynucleotide encoding an amino-terminal-modified chemokine, wherein the amino-terminal-modified chemokine comprises at least one methionine, at least one aminooxypentane residue, or at least one GroHEK peptide covalently attached to the amino terminus of the chemokine, and wherein the amino-terminal-modified chemokine is derived from a chemokine selected from the group consisting of SDF-1α, SDF-1β, IP-10, Mig, GROα, GROβ, GROγ, interleukin-8, PF4, ENA-78, GCP-2, PBP, CTAP-III, β-thromboglobulin, NAP-2, C10, DC-CK1, CKα1, CKα2, MCP-1, MCP-2, MCP-3, MCP-4, MIP-1α, MIP-1β, lymphotactin, ATAC, eotaxin, eotaxin-2, I-309, HCC-1, HCC-2, HCC-3, LARC/MIP-3α, MIP-3β, PARC, TARC, 6Ckine, ELC, SLC, CKβ4, CKβ6, CKβ7, CKβ8, CKβ9, CKβ11, CKβ12, CKβ13, and CX3C.

6. The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:6;
(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the

polynucleotide encoding met-hDSF-1α deposited under accession number ATCC 98506;

(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:10;

(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 10;

(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and

(f) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(e) above.

7. The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the polynucleotide encoding met-hDSF-1β deposited under accession number ATCC 98506;

(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:11;

(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 11;

(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and

(f) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(e) above.

8. The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8;

(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the polynucleotide encoding GroHEK/hSDF-1α deposited under accession number ATCC 98508;

(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:12;

(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 12;

(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and

(f) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(e) above.

9. The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;
(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the polynucleotide encoding GroHEK/hSDF-1β deposited under accession number ATCC 98509;
(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:13;
(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 13;
(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and
(f) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(e) above.

10. A composition of claim 1 wherein the polynucleotide is operably linked to an expression control sequence.

11. The composition of claim 10 wherein the polynucleotide is further operably to a sequence directing secretion if the expressed amino-terminal-modified chemokine.

12. A host cell transformed with a composition of claim 10.

13. The host cell of claim 12, wherein the cell is a mammalian cell.

14. A process for producing an amino-terminal-modified chemokine, which comprises:

(a) growing a culture of the host cell of claim 12 in a suitable culture medium; and
(b) purifying the amino-terminal-modified chemokine from the culture.

17. A composition comprising an isolated polynucleotide encoding an amino-terminal-modified chemokine, wherein the chemokine binds the fusin/CXCR4 chemokine receptor.

18. A composition comprising an isolated polynucleotide encoding an amino-terminal-modified chemokine, wherein the amino-terminal-modified chemokine is a more effective inhibitor of HIV infection than the corresponding unmodified chemokine.

50657-5302 US PT

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/175,713	10/20/98	HERRMANN S	GI-5302-CON

HM22/0730

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EXAMINER

ANDRES, T

ART UNIT	PAPER NUMBER
1646	14

DATE MAILED: 07/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

ACTION DOCKETED
Advisory Action
DUE DATE
September 2, 2001 (w/1ST extension)
By ____ On 9/3/01
w/2nd ext: 10/2/01
Appeal Deadline: 11/2/01

RECEIVED
AUG 01 2001
Jenkens & Gilchrist

PTO-90C (Rev. 2/95)
*U.S. GPO: 2000-473-000/44602

2 - Mail Copy

Advisory Action	Application No. 09/175,713	Applicant(s) HERRMANN ET AL.	
	Examiner Janet L Andres	Art Unit 1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 10 July 2001 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-14,17 and 18*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other:

Yvonne Eyler

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Continuation of 5. does NOT place the application in condition for allowance because: 1. Applicant argues that adequate written description is provided because the claims are drawn to a specifically enumerated set of amino-terminal modified chemokines. Applicant argues that the claims are drawn to compositions, rather than their functional characteristics and it is impermissible to read a functional limitation into the claims. Applicant's arguments are not found persuasive because Applicant states on page one of the specification that the invention relates to amino-terminal modified chemokines and the use of such chemokines to inhibit the interaction between chemokine receptors and naturally occurring ligands (lines 11-13). Thus the functional characteristics of the claimed molecules are essential to what Applicant has described on the first page and throughout the specification as the invention. Further, the claims are drawn to molecules "comprising at least one" of a number of possible modifications and thus are not "specifically enumerated"; the open language encompasses a potentially infinite number of species. Since both the chemokines and the modifications claimed encompass structurally unrelated molecules, the species are, as stated in the previous Office Action, widely diverse. Thus a description of the common attributes or features of inhibitory chemokines is not set forth, and one of skill would not recognize that Applicant was in possession of the invention described in the specification.

2. Applicant argues that the specification is enabling for the invention because all that is required is knowledge of the nucleotide sequences of the listed chemokines along with a method of producing the amino-terminal modified form of one of the chemokines. Applicant argues that as long as the specification discloses at least one method for making and using the invention that bears a reasonable correlation to the entire scope of the claim the enablement requirement is satisfied. Applicant's arguments are not found persuasive because they are not commensurate with the scope of the claims. What is set forth in the specification as Applicant's invention are amino-terminally modified molecules that are inhibitors of receptor/ligand binding. Enablement of the claimed invention requires that Applicant teach both how to make and use it. As stated above and in the previous Office Actions, the claims encompass many different and structurally varied molecules, including sequences with internal variations. Since the prior art teaches that the effects of the claimed modifications are unpredictable, one of skill in the art would not be able to predict which of the many possible modified chemokines would function in accordance with what Applicant has described as the invention. Thus one of skill in the art would be able to make the modified proteins, but would not be able to predict which could actually be used. It is this lack of predictablility as to which of the many possible embodiments of the claims would function as Applicant has described that renders the required experimentation undue.

3. Applicant argues that the claims are not indefinite because "fragments" and "stringent hybridizing conditions" are defined in the specification. Applicant argues that the statement on p. 20 is a definition of "fragment". This is not found persuasive because the statement requires that the fragment "retain the desired activity" or "modify it to create a desired activity". There is no limitation as to what such desired activities might encompass and Applicant has in fact argued that no such limitations are required by the claims. Thus one of skill in the art would not be able to determine what such fragments might be. Applicant further argues that stringent conditions are defined on p. 22. This is not found persuasive because, as stated in the previous office action, the conditions provided are merely examples. See p. 22, line 14: "highly stringent conditions include, for example..." and line 16, "Preferably, such hybridizing polynucleotides...".

Attachment for PTO-948 (Rev. 03/01, or earlier)
6/18/01

The below text replaces the pre-printed text under the heading, "Information on How to Effect Drawing Changes," on the back of the PTO-948 (Rev. 03/01, or earlier) form.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the Notice of Allowability Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136(a) or (b) for filing the corrected drawings after the mailing of a Notice of Allowability The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes

Timing of Corrections

Applicant is required to submit the drawing corrections within the time period set in the attached Office communication See 37 CFR 1.85(a).

Failure to take corrective action within the set period will result in **ABANDONMENT** of the application

PATENT APPLICATION
Docket No.: 50657-05302USP1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Hermann et. al.	§	Art Unit:	1646
		§		
Serial No.:	09/175,713	§	Examiner:	Janet L. Andres
		§		
Filed:	October 20, 1998	§		
		§		
Entitled:	Chemokines with Amino-Terminal Modifications	§		
		§		

CERTIFICATE OF MAILING 37 C.F.R. 1.10

"EXPRESS MAIL" Mailing Label No. EL 916517477 US
Date of Deposit: October 18, 2001
I hereby certify that this paper or fee is being deposited with the U.S. Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231

Type or Print Name: Rosemary Bell

Rosemary Bell
Signature

Box AF
Assistant Commissioner for Patents
Washington, DC 20231

Dear Sir:

RESPONSE TO ADVISORY ACTION MAILED JULY 30, 2001

In response to the Advisory Action mailed on July 30, 2001, Applicants respectfully respond as follows.

AMENDMENTS

In the claims:

Please amend the claims as follows:

6. (Amended) The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:6;

(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the polynucleotide encoding met-hDSF-1α deposited under accession number ATCC 98506;

(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:10;

(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 10;

(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and

(f) a polynucleotide capable of hybridizing at either (i) 4xSSC at 65°C or (ii) 50% formamide and 4XSSC at 42°C, to any one of the polynucleotides specified in (a)-(e) above.

7. (Amended) The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the polynucleotide encoding met-hDSF-1β deposited under accession number ATCC 98506;

(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:11;

(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 11;

(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and

(f) a polynucleotide capable of hybridizing at either (i) 4xSSC at 65°C or (ii) 50% formamide and 4XSSC at 42°C, to any one of the polynucleotides specified in (a)-(e) above.

8. (Amended) The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8;

(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the polynucleotide encoding GroHEK/hSDF-1α deposited under accession number ATCC 98508;

(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:12;

(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 12;

(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and

(f) a polynucleotide capable of hybridizing at either (i) 4xSSC at 65°C or (ii) 50% formamide and 4XSSC at 42°C, to any one of the polynucleotides specified in (a)-(e) above.

9. (Amended) The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the polynucleotide encoding GroHEK/hSDF-1β deposited under accession number ATCC 98509;

(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:13;

(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 13;

(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and

(f) a polynucleotide capable of hybridizing at either (i) 4xSSC at 65°C or (ii) 50% formamide and 4XSSC at 42°C, to any one of the polynucleotides specified in (a)-(e) above.

REMARKS

Claims 1-14, 17 and 18 are pending in the Application. Claims 1-14, 17 and 18 stand rejected in the Advisory Action mailed on July 30, 2001. Claims 6-9 have been amended. Appendix A at page 7 of this Paper provides a marked-up copy of the amended claims in accordance with 37 C.F.R. 1.121(c). Appendix B at page 9 of this Paper lists all of the pending claims (with amendments) for Examiner's convenience.

Applicants have amended claims 6-9 to address Examiner's rejections of the claims as indefinite with respect to the use of the term "stringent hybridization conditions" in the claims. Without

acquiescing to the propriety of Examiner's rejection, Applicants have replaced the term "stringent hybridization conditions" with language reciting specific hybridization conditions. Support for the amendment can be found in the Specification at page 22, lines 15-16.

No new matter has been added as a result of these amendments.

RESPONSE TO THE REJECTION OF CLAIMS 1-14, 17 AND 18

Applicants respectfully disagree with Examiner's rejection of claims 1-14, 17 and 18. In accordance with 37 C.F.R. § 1.114 (c), Applicants have filed a Notice of Appeal which is being concurrently filed with this Paper.

A Petition for Extension of Time (Three Months) and the requisite fee ($ 920) are attached. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 10-0447 (Reference No.: 50657-05302USP1).

PATENT APPLICATION
Docket No.: 50657-05302USP1

Respectfully submitted,

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Appendix A
Marked-up copy of amended claims

6. (Amended) The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:6;
(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the polynucleotide encoding met-hDSF-1α deposited under accession number ATCC 98506;
(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:10;
(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 10;
(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and
(f) a polynucleotide capable of hybridizing [under stringent conditions] at either (i) 4xSSC at 65°C or (ii) 50% formamide and 4xSSC at 42°C, to any one of the polynucleotides specified in (a)-(e) above.

7. (Amended) The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;
(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the polynucleotide encoding met-hDSF-1β deposited under accession number ATCC 98506;
(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:11;
(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 11;
(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and
(f) a polynucleotide capable of hybridizing [under stringent conditions] at either (i) 4xSSC at 65°C or (ii) 50% formamide and 4XSSC at 42°C, to any one of the polynucleotides specified in (a)-(e) above.

8. (Amended) The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8;

(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the polynucleotide encoding GroHEK/hSDF-1α deposited under accession number ATCC 98508;

(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:12;

(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 12;

(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and

(f) a polynucleotide capable of hybridizing [under stringent conditions] at either (i) 4xSSC at 65°C or (ii) 50% formamide and 4XSSC at 42°C, to any one of the polynucleotides specified in (a)-(e) above.

9. (Amended) The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the polynucleotide encoding GroHEK/hSDF-1β deposited under accession number ATCC 98509;

(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:13;

(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 13;

(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and

(f) a polynucleotide capable of hybridizing [under stringent conditions] at either (i) 4xSSC at 65°C or (ii) 50% formamide and 4XSSC at 42°C, to any one of the polynucleotides specified in (a)-(e) above.

Appendix B
List of Pending Claims

1. (Amended) A composition comprising an isolated polynucleotide encoding an amino-terminal-modified chemokine, wherein the amino-terminal-modified chemokine comprises at least one methionine, at least one aminooxypentane residue, or at least one GroHEK peptide covalently attached to the amino terminus of the chemokine, and wherein the chemokine is selected from the group consisting of SDF-1α, SDF-1β, IP-10, Mig, GROα, GROβ, GROγ, interleukin-8, PF4, ENA-78, GCP-2, PBP, CTAP-III, β-thromboglobulin, NAP-2, C10, DC-CK1, CKα1, CKα2, MCP-1, MCP-2, MCP-3, MCP-4, MIP-1α, MIP-1β, lymphotactin, ATAC, eotaxin, eotaxin-2, I-309, HCC-1, HCC-2, HCC-3, LARC/MIP-3α, MIP-3β, PARC, TARC, 6Ckine, ELC, SLC, CKβ4, CKβ6, CKβ7, CKβ8, CKβ9, CKβ11, CKβ12, CKβ13, and CX3C.

2. The composition of claim 1 wherein the amino-terminal-modified chemokine comprises at least one methionine covalently attached to the amino terminus of the chemokine.

3. The composition of claim 1 wherein the amino-terminal-modified chemokine comprises at least one aminooxypentane residue covalently attached to the amino terminus of the chemokine.

4. The composition of claim 1 wherein the amino-terminal-modified chemokine comprises at least one GroHEK peptide covalently attached to the amino terminus of the chemokine.

5. (Amended) A composition comprising an isolated polynucleotide encoding an amino-terminal-modified chemokine, wherein the amino-terminal-modified chemokine comprises at least one methionine, at least one aminooxypentane residue, or at least one GroHEK peptide covalently attached to the amino terminus of the chemokine, and wherein the amino-terminal-modified chemokine is derived from a chemokine selected from the group consisting of SDF-1α, SDF-1β, IP-10, Mig, GROα, GROβ, GROγ, interleukin-8, PF4, ENA-78, GCP-2, PBP, CTAP-III, β-thromboglobulin, NAP-2, C10, DC-CK1, CKα1, CKα2, MCP-1, MCP-2, MCP-3, MCP-4, MIP-1α, MIP-1β, lymphotactin, ATAC, eotaxin, eotaxin-2, I-309, HCC-1, HCC-2, HCC-3, LARC/MIP-3α, MIP-3β, PARC, TARC, 6Ckine, ELC, SLC, CKβ4, CKβ6, CKβ7, CKβ8, CKβ9, CKβ11, CKβ12, CKβ13, and CX3C.

6. (Amended) The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:6;

(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the

polynucleotide encoding met-hDSF-1α deposited under accession number ATCC 98506;

(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:10;

(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 10;

(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and

(f) a polynucleotide capable of hybridizing at either (i) 4xSSC at 65°C or (ii) 50% formamide and 4XSSC at 42°C, to any one of the polynucleotides specified in (a)-(e) above.

7. (Amended) The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the polynucleotide encoding met-hDSF-1β deposited under accession number ATCC 98506;

(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:11;

(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 11;

(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and

(f) a polynucleotide capable of hybridizing at either (i) 4xSSC at 65°C or (ii) 50% formamide and 4XSSC at 42°C, to any one of the polynucleotides specified in (a)-(e) above.

8. (Amended) The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8;

(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the polynucleotide encoding GroHEK/hSDF-1α deposited under accession number ATCC 98508;

(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:12;

(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 12;

(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and

(f) a polynucleotide capable of hybridizing at either (i) 4xSSC at 65°C or (ii) 50% formamide and 4XSSC at 42°C, to any one of the polynucleotides specified in (a)-(e) above.

9. (Amended) The composition of claim 1 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of the protein-coding sequence of the polynucleotide encoding GroHEK/hSDF-1β deposited under accession number ATCC 98509;

(c) a polynucleotide encoding an amino-terminal-modified chemokine comprising the amino acid sequence of SEQ ID NO:13;

(d) a polynucleotide encoding a protein comprising an amino-terminal fragment of the amino acid sequence of SEQ ID NO: 13;

(e) a polynucleotide comprising a nucleotide sequence complementary to any one of the polynucleotides specified in (a)-(d) above; and

(f) a polynucleotide capable of hybridizing at either (i) 4xSSC at 65°C or (ii) 50% formamide and 4XSSC at 42°C, to any one of the polynucleotides specified in (a)-(e) above.

10. A composition of claim 1 wherein the polynucleotide is operably linked to an expression control sequence.

11. The composition of claim 10 wherein the polynucleotide is further operably to a sequence directing secretion if the expressed amino-terminal-modified chemokine.

12. A host cell transformed with a composition of claim 10.

13. The host cell of claim 12, wherein the cell is a mammalian cell.

14. A process for producing an amino-terminal-modified chemokine, which comprises:

(a) growing a culture of the host cell of claim 12 in a suitable culture medium; and

(b) purifying the amino-terminal-modified chemokine from the culture.

17. A composition comprising an isolated polynucleotide encoding an amino-terminal-modified chemokine, wherein the chemokine binds the fusin/CXCR4 chemokine receptor.

18. A composition comprising an isolated polynucleotide encoding an amino-terminal-modified chemokine, wherein the amino-terminal-modified chemokine is a more effective inhibitor of HIV infection than the corresponding unmodified chemokine.